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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,898	OLEK ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *35-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-31 and 35-42* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' elections with traverse of Group I (claims 1-31) and the following species: A (at least one individual), E (at least one individual), dissection, histological sample, K (from both healthy and diseased individuals), N (samples taken after treatment only), complete genes and/or promoters, and cancer, filed 10/14/04, are acknowledged. Amended claims 1, 3-31, 35, 37, and 39-42 as well as cancelled claims 32-34 are acknowledged. Claims 35-42 are withdrawn from consideration as being drawn to non-elected Groups.

Applicants' traversal is on the grounds that a search of Groups I and IV as well as additional species would not pose undue burden on the Patent Office.

The applicants' request to combine Groups I, III, and IV into one invention as well as searching additional species was found unpersuasive because of the following reasons (summarized from the restriction paper):

Groups I, III, and IV are related as product and processes of use. The composition of Group III may be used in the methods of Groups I and IV, or alternatively in lead computer modeling. All of these usages are distinct as requiring distinct and different functions thereof. In addition the methods in Groups I and IV contain method steps that are not required one for the other. These differences illustrate distinct differences that affect the outcome of the methods making them different with divergent subject matter which supports the requirement for restriction.

It is appreciated that Applicants elected one specie for each specie election requirement. It is noted that such species election requirements were requested simply to narrow down the examination at this time in compact prosecution. It is also noted that if the elected species are held to be allowable, then the specie election requirements will be withdrawn such that all species will be examined for that particular specie election requirement. Applicants suggest the different categories of species A-D are not mutually exclusive and would not pose an undue burden in searching. This statement is found unpersuasive as biological samples from different parts of a body, such as a tissue, cell, or broadly from an individual, requires different methodology as these represent different focal points further demonstrating divergent subject matter. Applicants state the Office has failed to explain why it would be an undue search burden to search and examine all of the different means of obtaining biological samples listed in claim 2. This statement is found unpersuasive as it was stated in the restriction paper that each obtainment means involves processes or steps that are different from other means, documenting the presence of divergent subject matter. Applicants state the Office has failed to explain why it would be an undue search burden to examine all different types of biological samples listed in 3. This statement is found unpersuasive as each contains distinct entities with structures and functions that differ from other entities, thus documenting the presence of divergent subject matter. Applicants argue that the remaining specie election requirements (fifth through eighth) lack explanation as to why an undue search burden would be present. These statements are all found unpersuasive as such explanation was provided in the second full paragraph of page 5 in the previous restriction paper. Applicants have failed to provide evidence suggesting that such

reasons would be considered improper, such that all Applicants' arguments are deemed unpersuasive.

The requirements are still deemed proper and are therefore made FINAL.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to methods, systems, and computer program products for determining the biological effect and/or activity of drugs, chemical substances and/or pharmaceutical compositions based on their effect on the methylation status of the DNA, whereas in contrast the elected claims are specifically directed to a method for determining the biological effect and/or activity of at least one drug, chemical substance, and/or pharmaceutical composition.

Claims herein under examination are 1-31.

Specification

The disclosure is objected to because of the following informalities: Pages 1-18 contain single spacing within paragraphs which is improper format. The specification should be presented in double spaced format. A substitute specification is requested with the appropriate corrections.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 1, line 5, recites the phrase "which was exposed to" which is vague and indefinite. It is unclear if the biological sample, the individual, or both were exposed to the said at least one drug. Clarification of the metes and bounds of the claim via clearer claim wording is requested. Claims 2-31 are also rejected due to their direct or indirect dependency from claim 1.

Claim 1, penultimate line, recites the phrase "concluding [...] on the biological effect and/or activity" which is vague and indefinite. It is clear that the conclusion is for the drug but it is unclear to what this effect and/or activity is directed. For example, the effect and/or activity can be directed to one of the individuals from step (a), it could be directed to cancer patients, or various other scenarios. Clarification of the metes and bounds of the claim via clearer claim wording is requested. Claims 2-31 are also rejected due to their direct or indirect dependency from claim 1.

Claims 1 (penultimate line) and 6 (line 3) recite the phrase "said at least one drug, chemical substance or pharmaceutical composition" which lacks clear antecedent basis as prior mention of these entities (claim 1, line 2) was made under an "and/or" scenario. Correction of this issue via clearer claim wording is requested. Claims 2-5 and 7-31 are also rejected due to their direct or indirect dependency from claim 1.

Claims 2-31 recite the phrase "according to" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "according to". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 2 (line 1), 3 (line 2), and 24 (line 2) recite the phrase "the biological sample" which lacks clear antecedent basis. It is unclear if the biological sample is referring to biological sample A or B or both from claim 1. Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 4 (line 2) and 8 (line 2) recite the phrase "said biological sample" which lacks clear antecedent basis. It is unclear if said biological sample is referring to biological sample A or B or both from claim 1. Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claim 5, lines 2-3, recites the phrase "identical individual, tissue, cell or other biological material". It is unclear if the "identical" characteristic only applies to the individual or also to the tissue, cell, or other biological material. Clarification of the metes and bounds of the claim via clearer claim wording is required. Claim 6 is also rejected due to its dependency from claim 5.

Claims 8 (line 4), 10 (line 2), and 13 (line 3) recite the phrase "the DNA" which lacks clear antecedent basis. It is unclear if the DNA is from sample A or B or both. Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 14 (line 3) and 15 (line 3) recite the phrase "related with" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "related with". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 17 (line 2) and 25 (line 2) recite the phrase "is based on" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be

considered "is based on". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 18 (line 2) and 19 (line 2) recite the phrase "performed in such a way as" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "performed in such a way as". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 19 (line 3), 20 (line 3), and 31 (line 3) recite the phrases "in particular", "such as", and "for example", respectively, which are indefinite claim language. These phrases render the claim indefinite because it is unclear whether the limitations following the phrases are part of the claimed invention. See MPEP § 2173.05(d). Clarification of this issue via clearer claim wording is requested.

Claim 28 (line 2) recites the phrase "the identical biological sample" which lacks clear antecedent basis. No prior mention in claim 1 was made of identical material. Correction of this issue via clearer claim wording is requested.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 13-21, 23-26, 28, and 31 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Laird et al. (P/N 6,331,393 B1).

Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A) (chemical substance) (abstract), as stated in instant claims 1, 9, and 13. Laird et al. disclose methylation amounts in a sample are quantitatively determined based on reference to a control reaction (sample B) (col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as stated in instant claim 1. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as stated in instant claim 1. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between MLH1 gene expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2 graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (col. 24, lines 48-67). Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (col. 1, lines 14-17) which represents cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite

(col. 5, lines 19-20 and 31). Laird et al. disclose various methods to identify altered methylation sites in cancer cells (col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal mucosa (healthy) tissue samples (Figures 7 and 8; col. 22, lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue in all normal and tumor samples (col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites are located in methylation relevant genes related with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sites of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA

samples are analyzed by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Altered DNA methylation pattern of cytosine residues is mutagenic (col. 2, lines 34-36) demonstrates the colorectal samples mentioned above represent genes related with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen) (col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (col. 9, lines 42-46). Laird et al. disclose using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (col. 14, lines 5-20) which represent selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as stated in instant claims 20, 26, and 31.

Thus, Laird et al. anticipate the limitations in claims 1-11, 13-21, 23-26, 28, and 31.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The

faxing of such papers must conform to the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

January 5, 2005

Ardin H. Marschel 1/7/05
ARDIN H. MARSCHEL
PRIMARY EXAMINER